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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/762,395	01/22/2004	Tony Giordano	051058-030100-DIV	4861

90162 7590 02/03/2010

David S. Resnick
Nixon Peabody LLP
100 Summer Street
Boston, MA 02110

EXAMINER	
LUNDGREN, JEFFREY S	

ART UNIT	PAPER NUMBER
1639	

MAIL DATE	DELIVERY MODE
02/03/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/762,395	GIORDANO ET AL.	
	Examiner	Art Unit	
	JEFFREY S. LUNDGREN	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/18/09*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *76,79-82,90,91,99,100,141 and 142* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *76, 79-82, 90, 91, 99, 100, 141 and 142* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claims 76, 79-82, 90, 91, 99, 100, 141 and 142 are pending in the instant application and are the subject of the Office Action below.

Claim Rejections - 35 USC § 112 – Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 76, 79-82, 90, 91, 99, 100, 141 and 142, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, Applicants are not enabled for the breadth of the claim that extends beyond the downregulation of PSA expression in human rhabdomyosarcoma cells using the 600 nt expression cassette (see Example 10), is maintained.

Applicants traverse the rejection and allege that the claimed method of using a vector to express a dsRNA is enabled for downregulating expression of a target gene in a RNA stress response competent cell.

Applicants contend that the factual basis for the rejection is improper because each of the references is not directed to an in vivo expression of the interference RNA:

> "Fire et al., Caplen et al., and Wianny et al. each teach delivering dsRNA by exogenous administration. That is, the dsRNA is produced in vitro and either transfected into a cell or injected directly into an organism. This is contrary to the present invention, that administers dsRNA by expressing the dsRNA in a cell from an expression vector."

Reply, page 4, last paragraph.

Applicants continue to allege that their working example and the remaining portions of their specification enable the invention in its entirety. Applicants further point to the work of

Robbins *et al.*, *Nature Biotechnology 24(5)*:566-571 (**2006**) as support that their claimed method is not limited to the working example.

The Examiner disagrees. First, the issues raised by Fire, Caplen and Wianny are not all a result of *in vitro* administration of the siRNA.

Secondly, Robbins is not comprehensive in its disclosure nor does it suggest that the full breadth of the claimed invention is enabled. For example, in rebuttal to Applicants' introduction to certain factual findings in Robbins, the Examiner provides Kenworthy *et al.*, *Nucleic Acids Research*, *37(19)*:6587-6599 (**2009**). In this publication, it is clear that the stress response is unpredictable and that the expression vector used did not avoid the stress response, contrary to what Applicants appear to be suggesting based on Robbins. See also, Bauer *et al.*, *Gene Ther., 16(1)*:142-147 (**2009**), in response to Applicants' reliance on Robbins, who states:

> "We show here that the induction of the interferonresponse gene Oas1 by expression of first generation shRNA can be abolished by the introduction of the targeting sequence into a miR-30 backbone, whereby the modification of the passenger strand seems to be a crucial feature to avoid innate cellular immune response."

Bauer, page 144, col. 1, second paragraph.

Applicants have not identified nor distinguished certain features that enable the full breadth of the claims, such as the shRNA or modification of the passenger strand, as done by Bauer, and therefore have left such undue experimentation at the feet of others.

Accordingly, the rejection is maintained.

Reiterated Rejection:

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". See *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Some of these factors may include:

(1) the breadth of the claims;
(2) the nature of the invention;
(3) the state of the prior art;
(4) the level of one of ordinary skill;
(5) the level of predictability in the art;

(6) the amount of direction provided by the inventor;
(7) the existence of working examples; and
(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims and the nature of the invention:

The claimed invention is overly broad because the claims read on all cells and all RNAs, including 21-mer siRNAs up to and beyond the 600 nucleotide RNA molecule demonstrated in Examples 10 and 11.

The amount of direction provided by the inventor and the existence of working examples:

Applicants generally state in their application that the claimed method can be carried out and only provide a working example that revolves around the use of downregulation of PSA expression in human rhabdomyosarcoma cells using the 600 nt expression cassette.

The level of unpredictability and the state of the art:

While it is recognized that introduction of dsRNA that is targeted to a specific gene may result in attenuation of expression of the targeted gene, the degree of attenuation and the length of time that attenuation is achieved is not predictable. For example, Fire (Trends in Genetics, 1999, vol. 15, p 358-363) teaches that post transcriptional gene silencing (PTGS) acts by decreasing the half-life of RNA. The natural stability of an RNA will have a quantitative influence upon its suitability as a PTGS target: naturally stable RNAs are likely to be more dramatically affected whereas RNAs that are rapidly synthesized and degraded might be less affected. Homeostatic regulation mechanisms might also influence the final outcome of PTGAS in that a decrease in the final product could activate a metabolic compensation mechanism that would partially restore expression level (see, p 360, second column, first paragraph). Fire (Nature 1998, vol. 391, p. 806-811) further indicates that introduction of dsRNA can result in a mosaic pattern of interference or resistance to interference may be observed. In addition, Fire teaches that the design of the dsRNA is important because not all dsRNA sequences work well. For example, dsRNA segments corresponding to various intron and promoter sequences do not

produce detectable interference (see p 809, second column). Fire also cautions that several limitations should be taken into account when designing RNA-interference-based experiments such as (1) a sequence shared between several closely related genes may interfere with several members of a gene family and (2) it is likely that a low level of expression will resist RNA-mediated interference for some or all genes and a small number of cells will likewise escape the effect of the interference (see page 810, first column, first full paragraph).

The disclosure of Caplen et al. (Gene 2000, vol. 252, p.95-105) provides additional evidence of the unpredictability of dsRNA attenuation/inhibition of a targeted gene in vertebrate cells in vitro. Caplen reports that although dsRNA inhibits gene expression in cultured *Drosophila* cells, screening of three commonly used cell lines from three different species: human, hamster, and mouse, using cells expressing transgenes both transiently and permanently, produced mixed results. Transient transfection of dsRNA targeted to the βgal transgene into 293 and BHK31 cells resulted either in no effect (293 cells) or a non-specific decrease in gene expression (BHK21 cells). Transfection of dsRNA into mouse NIH/3T3 cells transduced with a retrovirus expressing βgal induced no detectable decrease in gene expression (see pages 102-103).

Wianny et al. (Nature Cell Biology 2000, vol.2 p.70-75) have reported that dsRNA can be used as a specific inhibitor of gene activity (targeted against c-mos in the oocyte and against E-cadherin or a GFP transgene in the early mouse embryo) in the mouse oocyte and preimplantation embryo without causing a general translation arrest. However, the authors indicate that it is possible that the early mouse embryo is incapable of an interferon response, resulting in general translation arrest and that there may still be difficulties in using RNAi at later stages (see page 73, under Discussion). Thus, the *Wianny clearly suggests that administering dsRNA to vertebrate systems, either in vitro or in vivo, to attenuate/inhibit target genes is not a reproducible or predictable art.*

At the time the instant application was filed, and even to date, nucleic acid based therapies were highly unpredictable. The field of RNA interference was in its infancy and gene specific dsRNA inhibition in mammalian cells was also highly unpredictable, even in cells in culture and the ability to inhibit gene expression was variable and unpredictable among different cells lines and different target genes. In particular, in mammalian cells, longer dsRNA

molecules were observed to cause the induction of the PKR response, resulting in cell apoptosis and non-specific mRNA expression inhibition. Examples in the literature demonstrate that in some organisms, including zebrafish and mice, the inhibition by double stranded RNA was unpredictable or transient (see for example Oates et al. or Wianny et al). Attempts to 'knock out' gene function in an organism using double stranded RNA administered at the embryonic stage have demonstrated that inhibition by double stranded RNA is transient, and function is regained after multiple cell divisions (see for example Wianny et al.).

Further, mammals, including humans, have demonstrated an immune response triggered by *even small amounts of double stranded RNA that would preclude the use of dsRNA in vivo* (whole organism) and in Xenopus an endogenous dsRAD activity would predict that dsRNA methods would not be effective (see for example Wianny et al. page 74). The field of RNA interference determined that shorter dsRNA molecules could overcome this PKR response, and resulted in a more predictable inhibitory response, however, guidance for the use of shorter dsRNAs, as discussed in the literature as necessary to more predictably apply the claimed methods, was not provided in the instant specification. Even with the advances made by the field of RNA interference, however, to induce inhibition by RNA interference in mammalian cells in culture, RNA interference is still recognized in the art as not enabled for therapeutic purposes. (See for example, Caplen (RNAi as a gene therapy approach. Expert Opin. Biol. Ther. 2003, Vol. 3, p575-586), Coburn et al. (siRNAs: a new wave of RNA-based therapeutics. Journal of Antimicrobial Chemotherapy. 2003, vol. 51, p753-756) and Agami et al., "RNAi and related mechanisms and their potential use for therapy" Current Opinion in Chemical Biology, 2002, Vol. 6, pages 829-834) for a review on the progression of RNA interference in mammalian cells and the state of the art of RNA interference for therapeutic purposes.)

The quantity of experimentation needed to make or use the claimed invention:

Accordingly, due the complexity and unpredictability in the art to RNA molecules that are selective for in vivo attenuation without inducing a stress response that otherwise produce a stress response when administered in vitro, would result in an undue burden upon those of ordinary skill in the art beyond the downregulation of PSA expression in human rhabdomyosarcoma cells using the 600 nt expression cassette.

Conclusions

No claim is allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

If Applicants should amend the claims, a complete and responsive reply will clearly identify where support can be found in the disclosure for each amendment. Applicants should point to the page and line numbers of the application corresponding to each amendment, and provide any statements that might help to identify support for the claimed invention (*e.g.*, if the amendment is not supported *in ipsis verbis*, clarification on the record may be helpful). Should Applicants present new claims, Applicants should clearly identify where support can be found in the disclosure.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Jeff Lundgren whose telephone number is 571-272-5541. The Examiner can normally be reached from 7:00 AM to 5:30 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Christopher Low, can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Jeffrey S. Lundgren/
Primary Examiner, Art Unit 1639